Ethical Issues in Research Involving Children

Alan R. Fleischman, M.D.

Senior Advisor, The New York Academy of Medicine

Chair, Federal Advisory Committee, National Children's Study
NICHD/NIH

and

Clinical Professor of Pediatrics
Clinical Professor of Epidemiology and Population Health
Albert Einstein College of Medicine

October 25, 2006

Ethical Issues in Research Involving Children

Is it ethical
to do research
involving children?

APRIL 22, 2002

Powell's Mission Impossible

TIME

HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO ...

HUMAN GUINEA PIGS

$3.95US
16>
10030
0 925679 8

www.time.com AOL Keyword: TIME

Ethical Issues in Research Involving Children

Recent Reports

- **unexpected deaths of normal volunteers**
- **alleged financial conflicts of interest**
- **closing of clinical research at major Universities**
- **Maryland court decision re: parental discretion to permit pediatric research**
- **allegations that pharmaceutical companies suppress negative data**
- **allegation that foster children were treated as guinea pigs in AIDS research**

Ethical Issues in Research Involving Children

Research Regulations Involving Children

- 1983 Final rule Subpart D
- 1997 FDA Modernization Act
- 1998 FDA Pediatric Rule
- 1998 NIH Policy and Guidelines on Inclusion of Children
- 2000 Children's Health Act
- 2001 FDA adopts Subpart D
- 2002 Best Pharmaceuticals for Children Act
- 2003 Pediatric Rule

Ethical Issues in Research Involving Children

Is it ethical to do research involving children?

- **Are we willing to place a child at any risk or discomfort today for the sake of other children who might benefit in the future?**

- **If so, how do we protect the children to assure they are not placed at undue risk?**

Children are Unique

- **Diseases**
- **Development**
- **Growth**
- **Metabolism**
- **Toxicity**

Why are studies avoided in Children?

- **Small number of subjects**
- **High costs**
- **Complex consent process**
- **Limited economic gain**
- **High liability risk**

Ethical Issues in Research Involving Children

The Nuremberg Code (1947)

"The voluntary consent of the human subject is absolutely essential."

Ethical Issues in Research Involving Children

Henry K. Beecher, M.D. (NEJM, 1966)

"*Ethics and Clinical Research*"

- **22 examples of published clinical research**
- **Many of the patients never had the risks explained**
- **Hundreds never knew they were subjects of research**

Ethical Issues in Research Involving Children

Is it ethical to do research involving children?

- **Paul Ramsey—Protestant theologian:**

  only if the research furthers the medical interests of the child

- **Richard McCormick—Catholic theologian:**

  parents may consent even if there is no therapeutic benefit

Ethical Issues in Research Involving Children

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978)

- The Belmont Report
- Research Involving Children
- Institutional Review Boards
- Research Involving those Institutionalized as Mentally Infirm

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Practice:**

  intervention to enhance the well-being of an individual patient

- **Research:**

  protocol to test a hypothesis and contribute to generalizable knowledge

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Beneficence**
- **Respect for Persons**
- **Justice**

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Beneficence:**

"effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children"

"research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices…that may turn out to be dangerous"

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Respect for Persons:**

  Individuals with capacity…
  treated as autonomous

  Persons with diminished autonomy…
  entitled to protection

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Justice:**

"Historically the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients."

Federal Policy for the Protection of Human Subjects (45 CFR46)

- **Subpart A: Basic Policies**
  Institutional Review Boards
  Informed consent

- **Subpart B: Pregnant women, fetuses, and neonates**

- **Subpart C: Prisoners**

- **Subpart D: Children**

Ethical Issues in Research Involving Children

- **Subpart B—Pregnant women, human fetuses and neonates**

  - nonviable neonate – *"a neonate after delivery that, although living is not viable"*

  - viable – *"being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration"*

  - research involving neonates of uncertain viability –

  -prospect of enhancing probability of survival, or

  -development of important knowledge and

  -there will be no added risk to the neonate

Federal Policy for the Protection of Human Subjects (45 CFR46)

- **Subpart A: Basic Policies**
  Institutional Review Boards
  Informed consent

- **Subpart B: Pregnant women, fetuses, and neonates**

- **Subpart C: Prisoners**

- **Subpart D: Children**

Federal Policy for the Protection of Human Subjects (45CFR46)

"Children"

"Children are persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

45 CFR §46.402

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§46.407)**

Federal Policy for the Protection of Human Subjects (45CFR46)

Minimal Risk

"That the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

45 CFR §46.102(i)

"*Ethical Conduct of Clinical Research Involving Children*"
Institute of Medicine of the National Academies -- 2004

Minimal risk:

- **Interpret minimal risk in relation to the normal experiences of average, healthy, normal children**
- **Minimal risk may vary with age but not social status, illness, or circumstances**
- **Focus on "equivalence of risk" in daily lives or experiences in routine physical or psychological exams or tests**
- **Minimize risks even when risks are minimal**

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§46.407)**

"*Ethical Conduct of Clinical Research Involving Children*"
Institute of Medicine of the National Academies -- 2004

Prospect of direct benefit:

- **Tangible positive outcome (e.g. cure of disease, relief of pain, increased mobility)**
- **Level of risk may be greater than minimal but balanced by the compensating benefit**
- **Collateral or indirect benefits are not considered prospect of direct benefit**
- **Gifts, payments, compensation are not considered prospect of direct benefit**

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§46.407)**

Federal Policy for the Protection of Human Subjects (45CFR46)

Minor Increase Over Minimal Risk

- **Experiences of subjects commensurate with actual or expected medical situations**
- **Likely to yield generalizable knowledge of vital importance about subject's disorder or condition**
- **Assent of child and permission of parents**

45 CFR §46.406

"*Ethical Conduct of Clinical Research Involving Children*"
Institute of Medicine of the National Academies -- 2004

Minor increase over minimal risk:

- **Slight increase beyond minimal risk (as defined in relation to normal children)**
- **Assess duration, probability, and magnitude**
- **Commensurability—reasonably comparable to known past or future experiences**
- **"Condition" refers to a set of physical, psychological, neurodevelopmental, or social characteristics that has been shown to affect health, well-being or risk of future health problem**

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§46.407)**

Federal Policy for the Protection of Human Subjects (45CFR46)

- **Subpart A (§46.1):**
  - **Basic Policy**
  - **IRBs**
  - **Informed consent**

Ethical Issues in Research Involving Children

Institutional Review Boards

- **Expertise in Pediatrics**
- **Knowledge of regulations**
- **Appropriate Community members**
- **Credentialing/Monitoring/Accountability**

Ethical Issues in Research Involving Children

Pediatric Informed Consent

- **Parental permission**
- **Child assent**

Ethical Issues in Research Involving Children

Child Assent in Research

- **Developmentally appropriate**
- **Inform about study from perspective of child's experience**
- **Elicit expression of willingness**

Ethical Issues in Research Involving Children

Adolescent Consent in Research

- **Emancipated minor**
- **Mature minor**

Ethical Issues in Research Involving Children

Adolescent Consent in Research

- **Parental permission (??)**
- **Adolescent consent/assent**

Federal Policy for the Protection of Human Subjects (45CFR46)

Waiver of Parental Permission

"If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects…it may waive the consent requirements…"

45 CFR §46.408(c)

Federal Policy for the Protection of Human Subjects (45CFR§46)

Wards

- No special requirements for §46.404 or §46.405
- Research under §46.406 and §46.407 only if:
  - Related to status as wards, or
  - Conducted in schools, camps, hospitals, institutions….where majority of children are NOT wards
  - Requires appointment of advocate

45 CFR §46.409